ABSTRACT

Cyclooxygenase-2 (COX-2) inhibitors are a subclass of nonsteroidal anti-inflammatory drugs (NSAIDs). The enzymes that produce prostaglandins are called cyclooxygenase (COX). There are two types of COX enzymes, Cyclooxygenase-2 (COX-2) and COX-2 that the both enzymes produce prostaglandins. It was discovered that prostaglandins could indeed be separated into two general classes which could loosely be regarded as good and bad prostaglandins, according to the structure of a particular enzyme involved in their biosynthesis, cyclooxygenase. Prostaglandins, whose synthesis involves the COX-1, are responsible for maintenance and protection of the gastrointestinal tract, while prostaglandins whose synthesis involves the COX-2, are responsible for inflammation and pain. Their use is associated with the side effects such as gastrointestinal and renal toxicity. The therapeutic anti-inflammatory action of NSAIDs is produced by the inhibition of COX-2, while the undesired side effects arise from inhibition of COX-1 activity. Thus, it was though those more selective COX-2 inhibitors would have reduced side effects. Based upon a number of selective COX-2 inhibitors were developed to reduce undesired side effects. This review highlights the several reports that attempt to design and synthesis of some classes of selective COX-2 inhibitors.

KEYWORDS:
Cyclooxygenase-2 inhibitors, Nonsteroidal antiinflammatory drugs, Celecoxib, Inflammation.

1. INTRODUCTION

Cyclooxygenase-2 (COX-2) inhibitors are a subclass of nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs work by reducing the production of prostaglandins, chemicals that promote inflammation, pain, and fever (Brzozowski et al., 2010; Çelik et al., 2013; Inoue et al., 2011; Kumar et al., 2013; Mould-Quevedo, 2013; Robinson et al., 2014; Turajane, 2010; Williams and Buvanendran, 2011). Prostaglandins also protect the lining of the stomach and intestines from the damaging effects of acid, promote blood clotting by activating platelets, and also affect kidney function (Lim et al., 2010; Lin et al., 2011). The enzymes that produce prostaglandins are called cyclooxygenase (COX). There are two types of COX enzymes, Cyclooxygenase-1 (COX-1) and COX-2. Both enzymes produce prostaglandins (Chen et al., 2015; Hahm, 2013; Lokwani et al., 2015; Ruan et al., 2011). Fig. 1 illustrated the chemical structure of some non-selective COX-1/COX-2 inhibitors and some selective COX-2 inhibitors. Prostaglandins whose synthesis involves the COX-1, are responsible for maintenance and protection of the gastrointestinal tract, while prostaglandins whose synthesis involves the COX-2, are responsible for inflammation and pain.

NSAIDs block the COX enzymes and reduce production of prostaglandins. Therefore, inflammation, pain, and fever are reduced by all COX inhibitors (Ashok et al., 2011; Morales et al., 2014; Ruan et al., 2011; Yang et al., 2013). Unlike older NSAIDs that block both COX-1 and COX-2, the newer COX-2 inhibitors only block the COX-2 enzyme. Since COX-2 inhibitors do not block COX-1. Nevertheless, COX-2 inhibitors are as effective as the older NSAIDs for treating inflammation, pain and fever. The COX-2 enzyme was discovered in 1988 by Daniel Simmons. COX-2 inhibitors are used for treating conditions that cause inflammation, mild to moderate pain, and fever. Examples include: sports injuries, osteoarthritis and menstrual cramps. Unlike aspirin, also an NSAID, they are not effective for preventing strokes and heart attacks in individuals at high risk for such events. COX-2 inhibitors have several side effects such as abdominal pain, headache, nausea, diarrhea, flatulence, and insomnia (Akram et al., 2013; Bradshaw, 2010; Groves et al., 2010). COX-2 inhibitors and other NSAIDs may increase the risk of heart attacks, stroke, and related conditions, which can be fatal. This risk may increase with duration of use and in patients who have underlying risk factors for disease of the heart and blood vessels. Consumption of COX-2 inhibitors such as celecoxib with aspirin or other NSAIDs (for example, ibuprofen, naproxen and etc.) may increase the occurrence of stomach and intestinal ulcers. It may be used with low dose aspirin. Alcohol consumption increases the risk of developing stomach ulcers when taking NSAIDs (Çelik et al., 2013; Kumar et al., 2013; Williams and Buvanendran, 2011). Celecoxib is the only
COX-2 inhibitor currently available in the worldwide. Rofecoxib and valdecoxib are no longer available because they increased the risk of heart attacks and strokes with long term use (Mould-Quevedo, 2013; Schuler et al., 2013; Setia et al., 2014; Shu et al., 2010; Takashima-Hirano et al., 2011; Yan et al., 2012; Zhang et al., 2010).

Both COX-1 and COX-2 exist as integral, membrane-bound proteins, located primarily on the lumenal side of the endoplasmatic reticulum (ER) and the nuclear envelope. Importantly, COX-2 is more concentrated in the latter position. Both enzymes share common mechanistic features as well as product-substrate profiles. They catalyze transformations with similar kinetics, although dihomo-γ-linolenic acid and eicosapentaenoic acid show a higher affinity to COX-2 (Joan, 2003). Structurally, human COX-1 and COX-2 occur as homodimers stabilized by hydrophobic interactions, and hydrogen and electrolytic bridges. They also exhibit as much as 63% amino acid identity. They vary in terms of their chain length and glycosylation patterns (Regulski et al.) (Fig. 2).

Fig. 1. Chemical structure of some non-selective COX-1/COX-2 inhibitors (1–3) and some selective COX-2 inhibitors (4–7).

Fig. 2. The secondary structure of cyclooxygenase 2 (COX-2) homodimer with the inhibitor (celecoxib) bound to the active site.
2. COX inhibitors nature

2.1. Natural COX inhibitors

The Cox-2 inhibitors, whether in the form of synthetic drugs or natural herbs, can help patients and their health care providers deal with the inflammation that results from any number of bodymind disorders that afflict people at present. In fact, incorporating natural versions of Cox-2 inhibitors into health care will probably always be helpful to patients (Abed et al., 2015; Li et al., 2011).

Stellatin isolated from Dysophylla stellata is a cyclooxygenase inhibitor. A study have been reported the synthesis and biological evaluation of new stellatin derivatives for COX-1, COX-2 inhibitory and anti-inflammatory activities (Gautam et al., 2011). Eight derivatives showed more pronounced COX-2 inhibition than stellatin and, two of synthesized compound exhibited the highest COX-2 inhibition. They also exhibited the significant anti-inflammatory activity and their anti-inflammatory effects were more than that of stellatin and indomethacin. Molecular docking study revealed the binding orientations of stellatin and its derivatives into the active sites of COX-1 and COX-2 and thereby helps to design the potent inhibitors. Fig. 3 showed chemical structure and binding of stellatin at the active site of COX-1 and COX-2 inhibitors.

![Fig. 3. Chemical structure and binding of stellatin at the active site of COX-1 (a) and COX-2 (b) inhibitors.](image)

Nepodin and chrysophanol, isolated from Rumex nepalensis roots, showed significant cyclooxygenase (COX) inhibitory activity. Fig. 4 showed chemical structure of nepodin and chrysophanol (Grover et al., 2014a; Grover et al., 2014b). Among the synthesized compounds, four nepodin and three chrysophanol derivatives displayed more pronounced COX-2 inhibition than their respective lead molecule. Further, compounds exhibited better anti-inflammatory activity than ibuprofen.

![Fig.4. Chemical structure of nepodin and chrysophanol](image)
Phytochemicals and anti-inflammatory activity were investigated by Abed et al. in the leaves of Pellacalyx saccardianus from the Rhizophoraceae family (Abed et al., 2015). The powdered leaves were extracted using methanol in a soxhlet extractor. Purification of the methanol extract yielded two new compounds. An anti-inflammatory assay using COX-2 revealed that β-amyrin palmitate possessed the highest inhibitory effect (96.8%) at the lowest concentration (0.01 mM), which was higher than that of the positive controls, resveratrol (90.2%, 0.01 mM) and indomethacin (79.20%, 100 mM). The difference between the structure of COX-1 and COX-2 and inhibitor connection are showed in Fig. 5.

Fig. 5. The difference between the structure of COX-1 and COX-2.

Phytochemicals and anti-inflammatory activity were investigated by Abed and coworkers in the leaves of Pellacalyx saccardianus from the Rhizophoraceae family. The powdered leaves were extracted using methanol in a soxhlet extractor. Purification of the methanol extract yielded two new compounds, with six known compounds, β-amyrin palmitate. An anti-inflammatory assay using COX-2 revealed that β-amyrin palmitate possessed the highest inhibitory effect (96.8%) at the lowest concentration (0.01 μM), which was higher than that of the positive controls, resveratrol (90.2%, 0.01 μM) and indomethacin (79.20%, 100 μM) (Abed et al., 2015).

2.2. synthetic COX inhibitors
Targeting synthetic COX-2 inhibitors is a promising alternative strategy to COX-2 expression by natural compounds for cancer chemoprevention and therapy (Al-Hourani et al., 2011; Al-Suwaidan et al., 2013; Al-Turki et al.; Alanazi et al., 2015; Alegaon et al., 2014; Arfaie and Zarghi, 2010; Bansal et al., 2014; Basile et al., 2012; Chen et al., 2015; Chu et al., 2013; Consalvi et al., 2015; El-Sayed et al., 2011; El-Sayed et al., 2012; Eren et al., 2010; Fioravanti et al., 2010; Firke and Bari, 2015; Gautam et al., 2011; Ghataki et al., 2014; Grover et al., 2014a; Grover et al., 2014b; Haider et al., 2014; Hayashi et al., 2011; Kaur et al., 2012; Kim et al., 2014; Lai et al., 2010; Lee et al., 2012; Lokwani et al., 2015; Lu et al., 2011; Qiu et al., 2012; Raghavendra et al., 2012; Ruan et al., 2011; Sharma et al., 2012; Takashima-Hirano et al., 2011; Tewari et al., 2014; Zhong et al., 2012; Zhong et al., 2011). Zarghi et al. introduced a new group COX-2 inhibitors containing methylsulfonyl derivatives (Arfaie and Zarghi, 2010; Soltani et al., 2010) (Fig. 6). This study showed that a new class of triaryl propanones can be prepared via a simple aldol condensation reaction and in this class of compounds COX inhibition is sensitive to the geometry of propanone and type of substituent at the C-3 of the propanone moiety. In other work, Su et al. two new type of COX-2 inhibitor containing nimesulide derivatives were synthesized (Su et al., 2010). The results showed that one of them decreased aromatase activity in breast cancer cells. They could also suppress androgen stimulated cell growth, but did not affect estrogen enhanced cell proliferation. Moreover, this type of COX-2 inhibitor effectively inhibited long-term estrogen deprived MCF-7aro cell growth. The
results indicate that effective compound could potentially overcome AI resistance in breast cancer cell and could be used as a lead to design more potent derivatives.

Fig. 6: Some representative examples of COXIBs (celecoxib and rofecoxib), Triarylolefines (3) and 1,3-diarylprop-2-en-1-ones (4) lead compounds and this group designed scaffolds.

New series of triazoles derivatives were designed, synthesized and evaluated by Abou-zeid et al. for their activity as anti-inflammatory agents (Al-Turki et al.). Three novel series of diaryl heterocyclic derivatives were synthesized by Eren et al. in 2010 (Eren et al., 2010). The results of biological evaluation revealed that especially compounds belonging to 1H-pyrazole series exhibited the highest activity compared to the analog series. In addition, the substitution of 1H-pyrazole as a suitable central ring template with the benzoxazole moiety can be suggested as an effective scaffold for further design of selective and potent COX-2 inhibitors.

In other work, Rossella Fioravanti research group, eighteen new 1-N-substituted-3, 5-diphenyl-2-pyrazoline derivatives have been synthesized and cyclooxygenase (COX-1 and COX-2) inhibitory activities have been evaluated (Fioravanti et al., 2010). The results of these biological assays showed that some of the new derivatives showed a good activity against COX-2. A series of 1,5-diaryl-substituted tetrazole derivatives was synthesized by Al-Hourani et al. (Al-Hourani et al., 2011). All compounds were evaluated by cyclooxygenase (COX) assays in vitro to determine COX-1 and COX-2 inhibitory potency and selectivity. The results showed that the determined COX-2 inhibitory potency of synthesized compounds is almost an order of magnitude lower in comparison with previously prepared 1,4-diaryl substituted 1,2,3-triazoles by this research group. In other work, Ashok et al. were investigated potency of non-steroidal antiinflammatory drugs (NSAIDs) in reduction of the risk of breast cancer through inhibition of COX-2 (Ashok et al., 2011). The results showed that selective COX-2 inhibitors and non-specific NSAIDs have chemo-preventive activity...
against breast cancer. The use of NSAIDs in cancer treatment is appealing for its other palliative properties and ease of use.

In other work, El-Sayed and coworkers were designed and synthesized new arylhydrazone derivatives and a series of 1,5-diphenyl pyrazoles from 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (El-Sayed et al., 2011). Fig. 7 showed representative examples of nonselective, selective COX-2 inhibitors and the designed arylhydrazones and pyrazoles COX-2 selective inhibitors. The biological tests showed that the new synthesized compounds with anti-inflammatory activities were less active than diclofenac against COX-1. However, new synthesized compounds showed reasonable inhibitory profiles against COX-2, indicating that they are selective inhibitors for COX-2. Moreover, the study showed that new synthesized were the most selective among the tested compounds with selectivity.

![Representative examples of nonselective (A), selective (B and C) COX-2 inhibitors and the designed arylhydrazones and pyrazoles COX-2 selective inhibitors (2–6).](image)

In other work, Lu et al. a series of pyridine acyl sulfonamide derivatives (1–24) have been designed and synthesized and their biological activities were also evaluated as potential (COX-2) inhibitors (Lu et al., 2011). Synthesis route of new COX-2 inhibitors compounds showed in Fig 8. Among all the synthesized compounds, several compounds displayed the most potent COX-2 inhibitory activity. Antitumor and anti-inflammatory assays indicated that several compounds owned high anti-proliferative activity against cancer cell lines as well as COX-2-derived prostaglandin E2 inhibitory activity. Docking simulation was performed to position compound into the COX-2 active site to determine the probable binding model. Moreover promising anti-inflammatory activities were also obtained by those compounds. Bioavailability and toxicity test revealed the compounds to be nontoxic with drug properties. The results of this study may find a leading compounds toward the development of new therapeutic agent to fight against cancer and inflammation.
Fig. 8. Synthesis route of new COX-2 inhibitors compounds.

Al-Hourani et al. a series of novel 5-substituted 1H-tetrazoles as cyclooxygenase-2 (COX-2) inhibitors was prepared via treatment of various diaryl amides with tetrachlorosilane-sodium azide (Al-Hourani et al., 2012). All compounds were tested in cyclooxygenase (COX) assays in vitro to determine COX-1 and COX-2 inhibitory potency and selectivity. Tetrazoles contained a methylsulfonyl or sulfonamide group as COX-2 pharmacophore displayed only low inhibitory potency towards COX-2.

In other work, Qiu and coworkers, a series of dihydro pyrazolyl thiazolinone derivatives have been synthesized and their biological activities were also evaluated as potential cyclooxygenase-2 (COX-2) inhibitors (Qiu et al., 2012). Among these compounds, compound 2-(3-(3,4-dimethylphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-one displayed the most potent COX-2 inhibitory activity, but weak to COX-1. Docking simulation was performed to position compound into the COX-2 active site to determine the probable binding model. Based on the preliminary results, compound with potent inhibitory activity and low toxicity would be a potential and selective anti-cyclooxygenase-2 agent (Fig 9).
In 2012, Sharma et al. a series of fluorobenzoylated di- and tripeptides as potential leads for the development of molecular probes for imaging of COX-2 expression was prepared according to standard Fmoc-based solid-phase peptide synthesis (Sharma et al., 2012). Fig. 10 show design route of fluorine-containing small peptides as COX-2 inhibitors containing an aromatic amino acid residue, a sulfur-containing amino acid residue and acidic amino acid at the C-terminal end. All peptides were assessed for their COX-2 inhibitory potency and selectivity profile in a fluorescence-based COX binding assay. Within the series of 15 peptides tested, cysteine-containing peptides have the most potent COX-2 inhibitors. Fluorobenzoylated some tripeptides displayed some COX-2 selectivity, whereas fluorobenzoylated some dipeptides were shown not to be COX-2 selective. Fluorobenzoylated tripeptide was further used in molecular modeling docking studies to determine the binding mode within the active site of the COX-2 enzyme.
Takahashi et al. in 2012 for the first time, the inhibitory effects of the synthetic serotonin analogues on COX (1 and 2) were evaluated (Takahashi and Miyazawa, 2012). Two serotonin derivatives showed inhibitory effect of COX (1 and 2). Especially, one of serotonin derivatives exhibited excellent inhibitions on COX-2 with extremely high potency. The inhibitory activities of cinnamic acid derivatives and serotonin were evaluated to clarify whether inhibitory activities of compound due to cinnamic acid moiety or serotonin moiety. Caffeic acid and N-caffeoyl serotonin exhibited selective inhibition of COX-2 compared to aspirin. Chu et al. in other work, a group of 3-amino-2-pyr ones were synthesized and their biological activities were evaluated for inhibiting cyclooxygenase (COX) activity (Chu et al., 2013). This study has led to the identification of COX-1-selective inhibitors. Among the tested compounds, one of the compound exhibited the most potent COX-1 inhibitory activity and COX-1 selectivity index.

The cyclooxygenase-2 (COX-2) isozyme is over-expressed in multiple types of cancer, relative to that in adjacent non-cancerous tissue, prompted this investigation to prepare a group of hybrid fluorescent conjugates wherein the COX inhibitors ibuprofen, (S)-naproxen, acetyl salicylic acid, a chlororofecoxib analog and celecoxib were coupled via a linker group to an acridone, dansyl or rhodamine B fluorophore. Bhardwaj et al. study showed that within this group of compounds, the ibuprofen-acridone conjugate showed potent and selective COX-2 inhibition, but its fluorescence emission was not suitable for fluorescent imaging of cancer cells that over-express the COX-2 isozyme (Bhardwaj et al., 2013). In comparison, the celecoxib-dansyl conjugate showed a slightly lower COX-2 potency and selectivity than the conjugate, and it possesses a better fluorescence emission. Ultimately, a celecoxib-rhodamine B conjugate that exhibited moderate COX-2 potency and selectivity having the best fluorescence emission emerged as the most promising biomarker for fluorescence imaging using a colon cancer cell line that over-expresses the COX-2 isozyme.

A group of cyclic imides was designed by Al-Suwaidan and coworkers for evaluation as a selective COX-2 inhibitors and investigated in vivo for their anti-inflammatory activity (Al-Suwaidan et al., 2013) (Fig. 11). Some of the compounds were proved to be potent COX-2 inhibitors. In vitro COX-1/COX-2 inhibition structure–activity studies identified one of the compounds has a highly potent, and an extremely selective comparable to celecoxib, COX-2 inhibitor that showed superior anti-inflammatory activity relative to diclofenac. Molecular modeling was carried out through docking the designed compounds into the COX-2 binding site to predict if these compounds have analogous binding mode to the COX-2 inhibitors. The study showed that the homosulfonamide fragment of one of the compounds inserted deep inside the pocket of the COX-2 active site. Docking study of the synthesized effective compounds into the active site of COX-2 revealed a similar binding mode to a selective COX-2 inhibitor.

![Fig. 11. Representative examples of nonselective (A) and selective COX-2 inhibitors (B, C and D) and the designed cyclic imides (E)](image-url)
A series of 1,3,4-trisubstituted pyrazole derivatives have been synthesized and evaluated by Alegaon et al. for their cyclooxygenase (COX-1 and COX-2) inhibitory activity (Alegaon et al., 2014). All of the compounds showed good inhibition of COX-2. Among these derivatives, one of the compounds was the most potent and selective COX-2 inhibitor, with a significant selectivity index. Molecular docking studies were carried out in order to predict the hypothetical binding mode of these compounds to the COX-2 isoenzyme. The result of present study suggests that pyrazole–thiadiazole hybrid could be an interesting approach for the design of new selective COX-2 inhibitory agents.

A novel series of 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazoles were designed and synthesized by Bansal for selective COX-2 inhibition with potent anti-inflammatory activity (Bansal et al., 2014). Among the compounds tested, (2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazole) compound was found to be the most potent inhibitor of COX-2 showing promising degree of anti-inflammatory activity in the carrageenan-induced rat paw edema model. The lead compound further showed suppression of acetic acid-induced writhes comparable to that of aspirin and gastrosparing profile superior to the aspirin. Molecular docking analysis displayed higher binding affinity of ligands towards COX-2 than COX-1 model.

![Docking figures of 3,5-di-tert-butyl-2-hydroxyphenylhydrazones in COX-2 protein cavity.](image)

Although dual inhibition of Cyclooxygenase-2 (COX-2) and 5-Lipoxygenase (5-LOX) enzymes is highly effective than targeting COX or LOX alone, there are only a few reports of examining such compounds in case of colorectal cancers (CRC). In other work in 2014, Ghatak et al. report that the novel di-tert-butyl phenol-based dual inhibitors that exhibit significant cytotoxicity against human CRC cell lines (Ghatak et al., 2014). Molecular docking studies revealed a good fit of these compounds in the COX-2 and 5-LOX protein cavities. Fig. 12 showed docking figures of 3,5-di-tert-butyl-2-hydroxyphenylhydrazones in COX-2 protein cavity. The inhibitors show significant inhibition of COX-2 and 5-LOX activities and are effective against a panel of human colon cancer cell lines including HCA-7, HT-29, SW480 and intestinal Apc10.1 cells as well as the hyaluronan synthase-2 (Has2) enzyme over-expressing colon cancer cells, through inhibition of the Hyaluronan/CD44v6 cell survival pathway. Western blot analysis and qRT-PCR analyses indicated that the di-tert-butyl phenol-based dual inhibitors reduce the expression of COX-2, 5-LOX, and CD44v6 in human colon cancer HCA-7 cells, while the combination of CD44v6shRNA and DTPSAL has an additional inhibitory effect on CD44v6 mRNA expression. The synergistic inhibitory effect of Celecoxib and Licofelone on CD44v6 mRNA expression suggests that the present dual inhibitors down-regulate cyclooxygenase and lipoxygenase enzymes through CD44v6. The compounds also exhibited enhanced antiproliferative potency compared to standard dual COX/LOX inhibitors.
inhibitor, viz. Licofelone. Importantly, the HA/CD44v6 antagonist CD44v6shRNA in combination with synthetic compounds had a sensitizing effect on the cancer cells which enhanced their antiproliferative potency, a finding which is crucial for the anti-proliferative potency of the novel synthetic di-tert-butyl phenol based dual COX–LOX inhibitors in colon cancer cells.

3. The effect of selective COX-2 inhibitor on cancer, inflammatory and Pregnancy

3.1. Antitumor effects of COX-2 inhibitor

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, fever, and inflammation. The anti-inflammatory effect of NSAIDs is mediated primarily through cyclooxygenase-2 (COX-2) inhibition, a mechanism also thought likely to reduce cancer risk by promoting apoptosis, and inhibiting mutagenesis and angiogenesis through reduced prostaglandin synthesis. The production of prostaglandin is dependent on catalysis by COX-2, which is shown to be over-expressed in approximately one-third of various cancers (Ashok et al., 2011; Bhardwaj et al., 2013; Bhattacharwa et al., 2011; Cerella et al., 2011; Cerella et al., 2010; Debuquoy et al., 2014; Ding et al., 2011; Gore et al., 2011; Kim et al., 2011; Kumar et al., 2013; Salimi et al., 2014; Schuler et al., 2013; Setia et al., 2014; Su et al., 2010; Tsuji et al., 2010; Yan et al., 2012; Yang et al., 2013; Zhong et al., 2012). Enzymatic inhibitors of pro-inflammatory COX-2 possess multiple anti-cancer effects, including chemosensitization. In a research, Cerella et al. have been analyzed the effects of three COX-2 enzyme inhibitors (nimesulide and celecoxib) on apoptosis in different hematopoietic cancer models (Cerella et al., 2011). Surprisingly, COX-2 inhibitors strongly prevent apoptosis induced by a panel of chemotherapeutic agents. Cyclooxygenase (COX)-2 and lipoxygenase (LOX)-5 are involved in carcinogenesis of pancreatic cancer. COX-2 inhibitor celecoxib displays inhibitory effects in pancreatic cancer cell growth. Recently, it has been reported that COX-2 inhibitor may not be able to suppress pancreatic tumor growth in vivo and its application is further limited by untoward side effects (Ding et al., 2011). They results imply that combined use of celecoxib and other compounds might be an effective way to treat clinical patients with pancreatic cancer. In other work, Sevigny et al. evaluated anti inflammation and anticancer effect of some compounds (Sevigny et al., 2012). Prostanoids play an important role in a variety of physiological and pathophysiological processes including inflammation and cancer.

Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors have been associated with lower incidence rates of some cancers. Because asbestos can cause chronic inflammation at the pleural and peritoneal surfaces the authors hypothesised that NSAID and COX-2 inhibitors would inhibit the development of asbestos-induced mesothelioma (Robinson et al., 2014). The results showed that aspirin did not alter the rate of disease development or increase the length of time that mice survived. Aspirin had a small but significant effect on disease latency but disease progression was not affected by the continued presence of the drug. The results showed that NSAIDs and COX-2 inhibitors do not moderate mesothelioma development or progression in a human cohort exposed to asbestos and this result is confirmed in an autochthonous mouse model. Novel dihydropyrazole sulfonamide derivatives (30–56) were designed, synthesized, and evaluated by Zhong and coworkers for their biological activities as COX-1 and COX-2 inhibitors. In vitro biological evaluation against three human tumor cell lines revealed that most target compounds showed antiproliferative activities. Among the compounds, one of the compounds exhibited the most potent and selective COX-2 inhibitor relative to the reference drugs celecoxib. Docking simulation was performed to position compound into the COX-2 active site and the result showed that one of the compounds could bind well at the COX-2 active site and it indicated that one of the compounds could be a potent and selective COX-2 inhibitor (Chen et al., 2015).

3.2. Anti-inflammatory activity of COX-2 inhibitor

The cyclooxygenase (COX) enzymes are chiefly responsible for the production of prostaglandins, a well-known mediator of inflammation, pain, and swelling. Many selective COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib, and etoricoxib are marketed as new generation NSAIDs. However, because of several cardiovascular adverse effects associated with coxibs, they have been voluntarily withdrawn from the market. Thus, novel COX-2 selective inhibitors having anti-inflammatory and analgesic activities with an improved safety profile is the need of the hour (Alanazi et al., 2015; Bansal et al., 2014; Birmingham and Buvanendran, 2014; El-Sayed et al., 2012; Firke and Bari, 2015; Gautam et al., 2011; Geng et al., 2011; Gupta et al., 2011; Haider et al., 2014; Härtig et al., 2013; Hayashi et al., 2011; Higuera et al., 2014; Li et al., 2011; Morales et al., 2014; Niu et al., 2014; Stepanović-Petrović et al., 2011; Tewari et al., 2014). In a research, a group of 30 cyclic imides was designed by Alanazi et al. for evaluation as a
selective COX-2 inhibitor and investigated in vivo for anti-inflammatory and analgesic activities (Alanazi et al., 2015). Some of the compounds exhibit optimal COX-2 inhibitory potency and selectivity index. In vitro COX-1/COX-2 inhibition structure activity studies identified some compound has a highly potent and an extremely selective comparable to celecoxib, COX-2 inhibitor that showed superior anti-inflammatory activity relative to diclofenac. Molecular Docking study of the synthesized compound into the active site of COX-2 revealed a similar binding mode to SC-558, a selective COX-2 inhibitor. In other work, Alanazi et al. a group of new 30 cyclic imides was designed for evaluation as a selective COX-2 inhibitor and investigated in vivo for anti-inflammatory and analgesic activities. Four Compounds exhibit optimal COX-2 inhibitory potency and selectivity index. In vitro COX-1/COX-2 inhibition structure activity studies identified one of the compounds as a highly potent and an extremely selective comparable to celecoxib, COX-2 inhibitor that showed superior anti-inflammatory activity relative to diclofenac. Molecular Docking study of the synthesized compound into the active site of COX-2 revealed a similar binding mode to selective COX-2 inhibitor. Docking study showed that the methoxy moieties of synthesized compounds inserted deep inside the 2-pocket of the COX-2 active site, where the O-atoms of such groups underwent an H-bonding interaction. Figure 13 showed docking of synthesized compounds into the active site of COX-2 (Alanazi et al., 2015).

Fig. 13. Left panel showed docking of one of the synthesized compounds into the active site of COX-2. Hydrogen bonds are shown in red. Right panel showed alignment of synthesized compound and selective inhibitor (green) in the active site of COX-2.

3.3. Pregnancy prevention of COX-2 inhibitor

Emergency contraception can prevent pregnancy after unanticipated intercourse or failure of a primary contraceptive method (McCann et al., 2013). Cyclooxygenase-2 inhibitors reduce prostaglandin synthesis and disrupt essential reproductive processes. Ultrasound studies in women demonstrated that oral COX-2 inhibitors can delay or prevent follicle collapse associated with ovulation. McCann and coworkers in a research showed that an oral administration of a COX-2 inhibitor can inhibit reproductive function with sufficient efficacy to prevent pregnancy in primates. The pregnancy rate with meloxicam administration using the emergency contraception model was 6.5%, significantly lower than the pregnancy rate of 33.3% when vehicle without meloxicam was administered (McCann et al., 2013). The Oral COX-2 inhibitor administration can prevent pregnancy after a single instance of breeding in primates. While meloxicam may be ineffective for regular contraception, pharmacological inhibition of COX-2 may be an effective method of emergency contraception for women.

4. CONCLUSIONS AND REMARKS

In the forthcoming years, it is very probable that the new compounds will be increasingly designed and synthesized in COX-2 inhibitor, which is highly desirable. In this review article, initially the principles of most COX-2 inhibitor design and synthesis have been described and then their applications have been reviewed.

ACKNOWLEDGEMENTS

The authors thank the Research Council of Islamic Azad University for the financial support.
REFERENCES


Mould-Quevedo J. (2013). PMS21 - Economic Outcomes For Celecoxib In Latin America: A Cost-Effectiveness Study Of Cox-2 Inhibitors Against Nsoids+Ppi For Adult Patients With Osteoarthritis And Rheumatoid Arthritis In Brazil, Mexico, Colombia, And Costa Rica. *Value in Health* 16(3), A221.


